On facts

'*Facts without ideas are just the sweepings of the brain and the memory*.' Don't you just wish you could come up with useful sayings like that? Bandolier certainly does, especially as it could sum up some of the topics in this month's issue. For those in need of the quote, it is from Vissarion Belinskii, a Russian essayist.

We could also consider JK Galbraith, famous for a host of pithy quotes. Two could run together, coupling: "*In any great organisation it is far, far safer to be wrong with the majority than to be right alone*" with "*the conventional view serves to protect us from the painful job of thinking*." When it comes to thinking about what we do every day, we have to be a bit more open, especially in a world where new facts rain down on us. It's either that or become a box-ticker.

So some new facts from Bandolier this month. Bandolier is exercised by the importance of adverse events, and when apparently new adverse events appear with much used therapies, like erectile dysfunction with statins, they need a close look. There is more evidence than there used to be.

New facts, too, about self-monitoring of blood glucose in type-2 diabetes. It is generally frowned upon, at least in the UK. An observational study of clinical practice, with large numbers and long follow up, suggests that doctors left to their own devices pick the right patients, and achieve very good results. New facts, too, from a meta-analysis of observational studies of coxibs, NSAIDs, and heart attack. No class effect, apparently, and it might just be that some guidance may have been putting more patients at risk.

If there is a theme, here, it may be at how one looks at evidence, and those difficult facts. Using inadequate evidence, or being blown about by the latest "fact", may just be counterproductive. To return to JK Galbraith: "*The great thing about being right is that you don't have to change your mind so often.*"

In this issue

STATINS AND ERECTILE DYSFUNCTION

A patient-led story, following a query from a patient. Do statins cause erectile dysfunction? At face value this seems highly improbable, given the huge number of men given statins over the last decade or so, and the increasing attention given to adverse events. But we know that there has been some association between statins and erectile dysfunction, so a quick literature survey seemed in order, following up on a systematic review from 2002 [1].

Systematic review [1]

The review process involved searching eight electronic databases for any reports linking erectile dysfunction or impotence in men with the use of cholesterol lowering drugs. National regulatory adverse drug reaction registers were also examined.

The review reported that:

- Case reports linked both fibrates and statins with erectile dysfunction in a small number of men.
- Review articles linked fibrates with erectile dysfunction.
- Data from randomised clinical trials showed no difference between simvastatin and placebo in the 4S study (37/1814 on simvastatin, 28/1803 on placebo), but erectile dysfunction was not reported in other randomised trials.
- One case-control study looked at the prevalence of erectile dysfunction in 339 patients attending a lipid clinic compared with matched controls. Both fibrates and statins were independent predictors of erectile dysfunction with odds ratios of about 1.5 [2].
- Regulatory agencies in Australia and the UK had yellow card reports of erectile dysfunction in men on lipid lowering drugs, both fibrates and statins. In a small number of men, withdrawal of the lipid-lowering drug and re-challenge resulted in recurrent symptoms, though the re-challenge was usually not blind.

Drug monitoring systems

In Spain and France [3], 75 cases of impotence associated with statins were identified. All had a temporal sequence. About 90% of men recovered potency on statin withdrawal, and in some cases impotence appeared again on re-challenge. All statins were implicated.

In Holland [4] eight men were identified with decreased libido shortly after starting statins, and in two in whom

testosterone was measured there was a large decrease in serum testosterone while on statins, with recovery of testosterone levels on stopping statin.

In 2003/4, the WHO Uppsala Monitoring Centre had 144 reports of decreased libido, and 498 reports of impotence.

Prospective cohort study

Eighty men were recruited and completed an international index of erectile function questionnaire (IIEF) before starting statins [5]. Their mean age was 61 years, and they had high rates of smoking, ischaemic heart disease, and diabetes, and most were receiving antiplatelet therapy.

Before starting statins, the median IIEF score was 21 out of a maximum of 25, and 43% of men had scores above 21, indicating no erectile dysfunction. After starting statins, the median IIEF score fell to 6.5 (Figure 1) and the percentage without erectile dysfunction fell to 21% (Figure 2). Over half of men had a fall in 5 or more points on IIEF with statins, and 22% experienced new onset erectile dysfunction.

Statins can improve erectile function

Erectile dysfunction is more common in men with cardiovascular risk factors, and some small studies indicate that statins can help. One was a small, but randomised and double blind comparison of atorvastatin and placebo in 12 men with erectile dysfunction and who were taking sildenafil [6]. After six weeks of statin, but not placebo therapy, the IIEF score increased with sildenafil, and all men on atorvastatin had improved confidence in obtaining and keeping an erection.

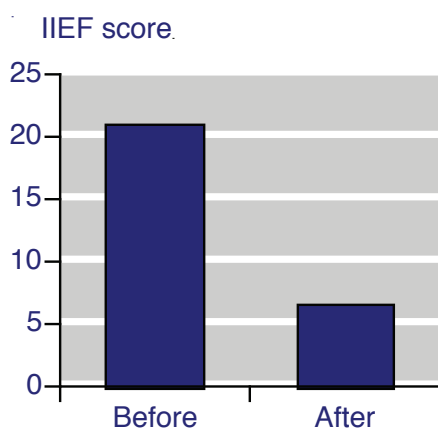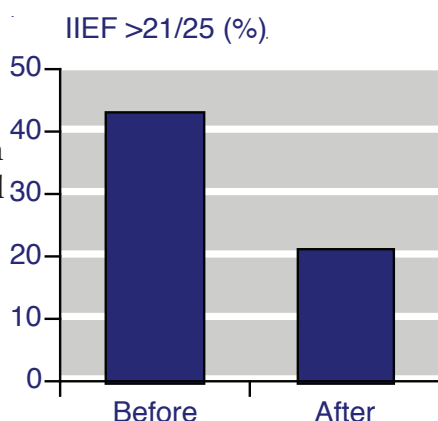**Figure 1: Change in IIEF before and after statins in cohort study**

Figure 2: Percentage of men with adequate erectile function score before and after statins in cohort study

Comment

We know that men with erectile dysfunction tend to have increased cardiovascular risk factors, including raised cholesterol. There are also studies showing that reducing cardiovascular risk factors, like losing weight, can improve erectile function. There is tentative evidence that cholesterol reduction with statins can also help erectile function.

That statins may also be the cause of erectile dysfunction is another matter, but the evidence does seem to be growing. To yellow card reporting in different countries can be added the prospective cohort study. Yet randomised trial results show no increase in erectile dysfunction rates with statins, and these were large trials, like 4S, conducted over a long period of time. In clinical practice, men may be different.

What is going on? The number of cases is small compared to the very widespread prescribing of lipid lowering drugs, especially statins. It is made more complicated by the average age of men reporting erectile dysfunction, mainly in their 50s when erectile dysfunction may occur anyway, and because many men using statins may be on therapy for other conditions. Though in most men testosterone metabolism in not affected by statin therapy, we have clear interference with testosterone biosynthesis in some of the affected men, and clear re-challenge evidence of the problem in others.

It looks as if this is a real problem for a small number of men. It is far too early to speculate on mechanisms, but testosterone synthesis needs cholesterol, and perhaps we should not be surprised that we may not all be average in the way our bodies work.

The good news is that the problem is reversible on stopping statins, and that drug switching helped in a number of cases. That just leaves the little problem of what to tell men when statins are needed.

References:

1 K Rizvi et al. Do lipid-lowering drugs cause erectile dysfunction? A systematic review. Family Practice 2002 19: 95-98.
2 E Bruckert et al. Men treated with hypolipidaemic drugs complain more frequently of erectile dysfunction. Journal of Clinical Pharmacology and Therapy 1996 21: 89-94.
3 A Carvajal et al. HMG CoA reductase inhibitors and impotence: two case series from the Spanish and French drug monitoring systems. Drug Safety 2006 29: 143-149.
4 L de Graaf et al. Is decreased libido associated with the use of HMG-CoA-reductase inhibitors? British Journal of Clinical Pharmacology 2004 58: 326-328.
5 H Solomon et al. Erectile dysfunction and statin treatment in high cardiovascular risk patients. International Journal of Clinical Practice 2006 60: 141-145.
6 HC Herrman et al. Can atorvastatin improve the response to sildenafil in men with erectile dysfunction not initially responsive to sildenafil? Hypothesis and pilot trial. Journal of Sexual Medicine 2006. Epub ahead of print. DOI: 10.1111/j.1743-6109.2005.00156.x

SMBG IN TYPE 2 DIABETES

Bandolier has revisited this topic on a number of occasions, whenever there appears to be something useful to add (Bandolier 84, 93, 134). The problem has been that in type 2 diabetes where insulin is not used, overwhelming evidence of benefit with self-monitoring of blood glucose (SMBG) is absent. We have a rash of small, short, largely pointless RCTs that tell us little. We have a number of observational studies, some strong, that indicate that SMBG is associated with lowering HbA$_{1c}$, and that this is a good thing that might save money. We can now add to these observational studies another long-term study [1] pointing to better clinical outcomes with SMBG.

Study

Information on 3,000 patients was obtained from 192 randomly selected practices in Germany. Patients included had to be over 45 years of age at time of diagnosis of type 2 diabetes (1995-1999), and have full information on therapy at the time of diagnosis and for at least one subsequent year. Patients were evaluated from diagnosis to an outcome or to the end of 2003.
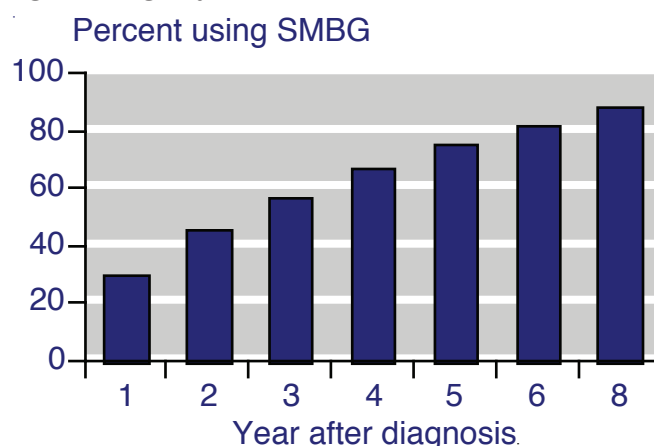
Predefined endpoints were nonfatal endpoints of myocardial infarction, blindness (one or both eyes), or renal failure requiring dialysis. All cause mortality was the other endpoint.

Results

Patients had an average age at baseline of 62 years, an average BMI of 30 kg/m^2, a fasting blood glucose of 9.3 mmol/L, and HbA$_{1c}$ of 7.7%. The average follow up was 6.5 years. After diagnosis of type 2 diabetes, over half of patients had no specific therapy, though this changed over the course of the observation period, with increases in insulin and oral hypoglycaemic therapy (Table 1).

Patients were allocated to the SMBG group if SMBG was documented for at least one year during the observation period and before a non-fatal endpoint. Overall, 45% of the total of 3,268 patients were classified as using SMBG, though the cumulative initiation of SMBG meant that most were using it by the end of the observation period (Figure 1). Pa-

Table 1: Treatments for type 2 diabetes after diagnosis and at the end of observation period (mean 6.5 years)

Treatment	Percent receiving treatment	
	Initial	End
No pharmacological treatment	54	13
Insulin monotherapy	2.9	17
Insulin + hypoglycaemic	2.4	16
Metformin (alone or + others)	19	43
Sulphonylureas	27	45

Figure 1: Cumulative initiation of SMBG during full eight years of observation

tients classified as using SMBG were significantly younger (by four years), and had higher fasting blood glucose (10 vs 8.7 mmol/L) and HbA$_{1c}$ (8.1 vs 7.2%).

For all patients, both fasting blood glucose and HbA$_{1c}$ levels fell over the first year. In those not using SMBG they rose slightly over subsequent years, while in those using SMBG the levels fell slightly. Fasting blood glucose and HbA$_{1c}$ levels were always significantly higher in SMBG users (HbA$_{1c}$ 7.2% vs 6.9% at end of observation, for instance).

Non-fatal endpoints

These were experienced by 293 patients (9% overall), with an incidence of 7.2% (107/1479) in those using SMBG and 10.4% (186/1789) in those not using SMBG, and the difference was present over the whole of the observation period.

In a subgroup of 2,500 who never received insulin, the incidence of non-fatal events was 6.7% (58/808) in those using SMBG and 10.4% (177/1707) in those not using SMBG. This reduction was due to a large decrease in macrovascular endpoints (heart attack, stroke, 6% vs 10%), while microvascular endpoints like amputation, dialysis, loss of vision occurred almost twice as often in the SMBG group (2.5% vs 1.5%).

All cause mortality

One hundred and twenty patients died (3.7% overall), with an incidence of 2.7% (41/1479) in those using SMBG and 4.6% (79/1789) in those not using SMBG, and the difference was present over the whole of the observation period.

In the subgroup never receiving insulin, death occurred in 2.5% (22/866) in those using SMBG and 4.3% (177/1649) in those not using SMBG.

Comment

Patients using SMBG were not the same as those who were not. They had worse diabetes, with higher fasting blood glucose and HbA$_{1c}$, and this difference remained over the course of observation, despite the use of SMBG. In consequence, the higher rate of microvascular complications was not unexpected.

The reduction in heart attacks and strokes, and in all cause mortality, for those using SMBG over those who were not, despite have less well controlled blood sugar and HbA_{1c} is interesting. After adjusting for possible confounding the study showed a 32% reduction in non-fatal endpoints and a 50% reduction in mortality. These are hard, important, clinical outcomes in a large cohort observed for a long period.

Of course, the patients were not randomised, but we will wait in vain for a randomised trial of this size and duration. Patients were assigned to SMBG by their doctors, and the evidence is that the doctors made a pretty good fist of it. They chose patients at greater risk, with worse diabetes, and their results were pretty good. They appeared to be maximising benefit while minimising costs. There may be lessons in this tale.

Reference:

1 S Martin et al. Self-monitoring of blood glucose in type 2 diabetes and long-term outcome: an epidemiological cohort study. Diabetalogia 2006 49: 271-278.

MI, COXIBS, AND NSAIDS

Bandolier makes no apology for returning to this subject for two reasons. First it is a topic of considerable interest, and second because it is an area in which there has been a very large amount of research, observational and randomised trial, and affords important insights into how we should evaluate evidence.

The first indication that there might be an association between NSAIDs or coxibs and cardiovascular events arose only in 2000, with the publication of a large RCT comparing rofecoxib with naproxen. Subsequent RCTs and observational studies produced mixed results, with some supporting an association, and others not. Complexities included different drugs, doses, duration of use, and arguments about class effects. New analyses from observational studies offer another opportunity to examine the evidence.

Overview of observational studies

A systematic review and meta-analysis of observational studies [1] sought observational studies published between 2000 and 2005, that included case-control and cohort studies of NSAID or coxib use and myocardial infarction, and that provided information to calculate a relative risk comparing users to nonusers.

Sixteen studies were included in the review. They had just over 3.5 million participants with 68,000 cases of myocardial infarction, so 2% of the population investigated had a heart attack. The outcome was typically first myocardial infarction, hospital admission for myocardial infarction, or coronary heart disease death, or combinations. Most studies used computerised pharmacy records or prescriptions, and the definition of exposure was primarily use at the index date or within periods from a few days to months.

Results of the pooled analysis, for all doses, are shown in Figure 1. Combining data for all traditional NSAIDs showed a significantly higher relative risk compared with nonusers. Among individual NSAIDs diclofenac and ibuprofen, but not naproxen, had significantly increased risk. For coxibs, rofecoxib had an increased risk, but not celecoxib.

Effect of dose

The same analysis [1] looked at the effect of dose for coxibs. For rofecoxib, doses of more than 25 mg daily produced a higher relative risk than doses within the licensed range of 12.5 to 25 mg daily (Table 1). For celecoxib there was no dose response.

Table 1: Effect of dose on relative risk of myocardial infarction with rofecoxib, by dose

Rofecoxib dose (mg per day)	Relative risk compared with nonusers (95% CI)
25 mg or less	1.2 (1.1-1.3)
more than 25 mg	1.8 (1.4 to 2.3)

Figure 1: Relative risk of myocardial infarction, hospital admission for myocardial infarction, or coronary death, according to use of NSAID or coxib (all doses) compared with non-use, in pooled analysis of 3.5 million patients
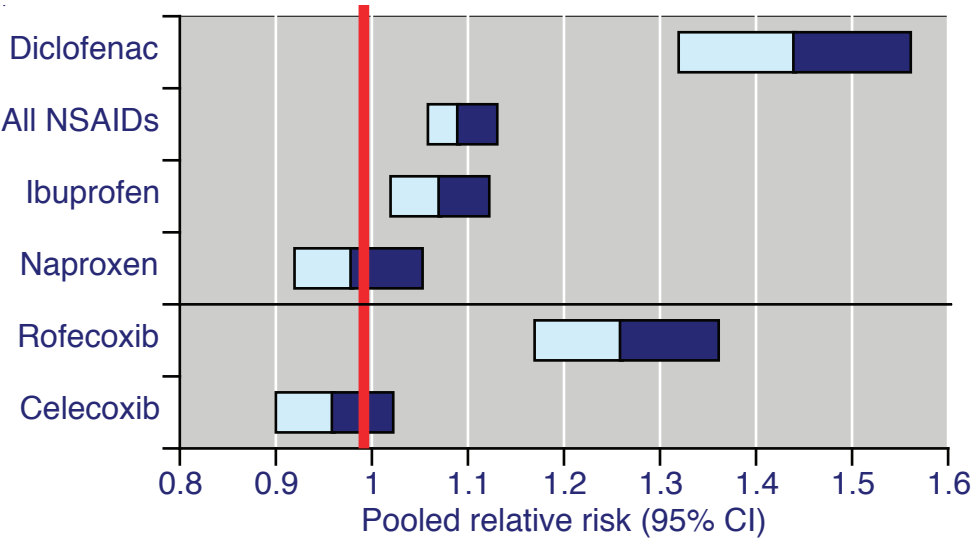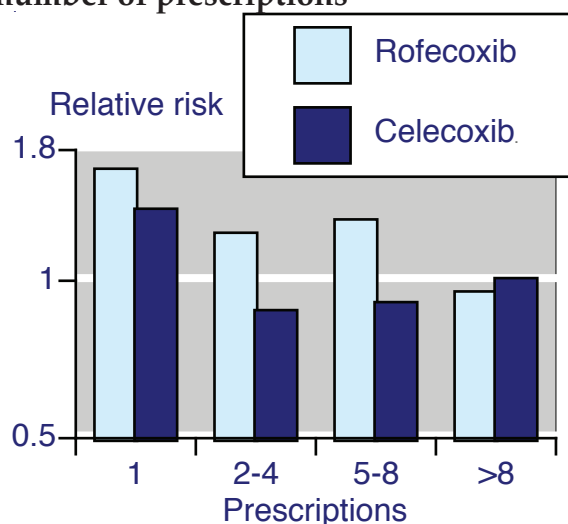
Figure 2: Relative risk of myocardial infarction by number of prescriptions


A large case-control study of the UK General Practice Research Database [2] confirmed a dose response for rofecoxib, and suggested a possible dose response for celecoxib, but based on a small number of actual events in users of higher doses of celecoxib. There was no evidence of dose response with any NSAID, though this analysis did confirm an elevated relative risk with diclofenac.

Duration of treatment

There is some evidence of a significantly increased risk of myocardial infarction with the first prescription of rofecoxib, but not celecoxib, in older people. A Canadian study [3] compared current users and nonusers. In the period of the first prescription (average duration 28 days), there was a significantly increased rate with rofecoxib (Figure 2), but not at any other time, or at any time with celecoxib.

By contrast, the UK GPRD study [2] had no increased rate of myocardial infarction with rofecoxib for duration of use less than three months, and showed no consistent duration effect with any drug where there was a sensible number of events.

Figure 3: Relative risk of myocardial infarction by levels of preexisting cardiovascular risk
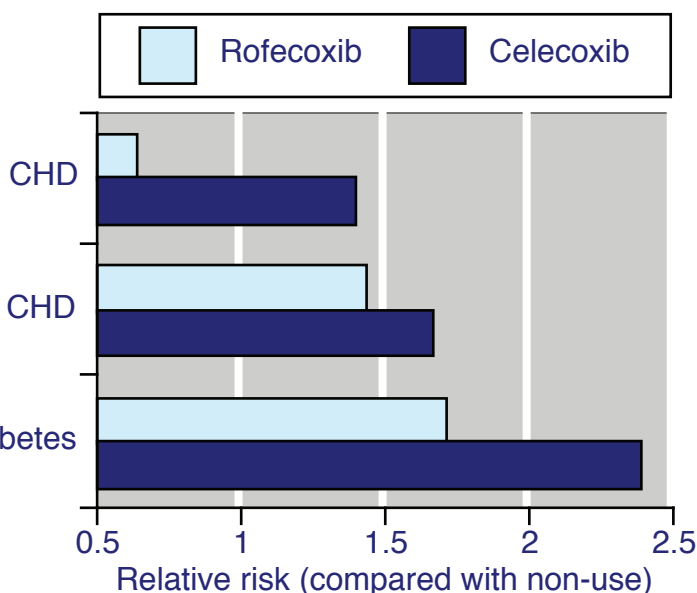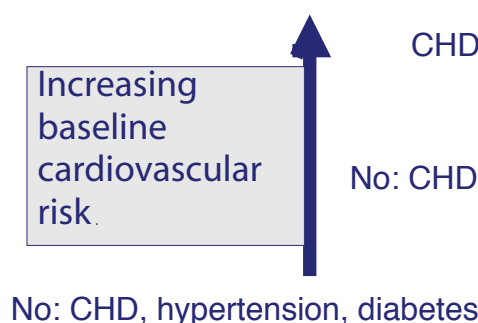
Cardiovascular risk

The UK GPRD study [2] looked at 3,643 cases of acute myocardial infarction among 490,000 people between 2000 and 2004. It examined the relative risk of myocardial infarction with current coxib use compared with nonusers according to the presence or absence of cardiovascular risk factors.

The results (Figure 3) show that for both rofecoxib and celecoxib there was no increased risk in people with coronary heart disease, and that the risk was highest in those users who did not have coronary heart disease, hypertension, or diabetes. Moreover, relative risks were higher in younger than in older people (Figure 4).

Comment

The evidence in these three studies, in over four million people and with over 70,000 myocardial infarctions means that we need to get our thinking caps on.

The first, and most obvious, thought is that we cannot keep on hiding behind the conventional idea that differences

Figure 4: Relative risk of myocardial infarction by age
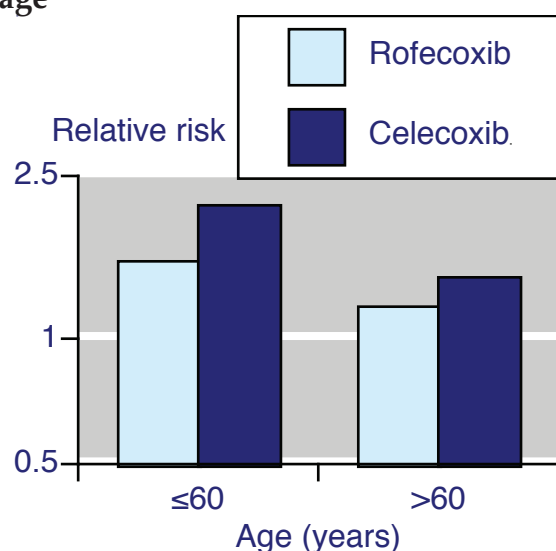
between traditional NSAIDs and coxibs constitute a class effect. Not as far as myocardial infarction is concerned, because at least one commonly used traditional NSAID, diclofenac, has apparently the highest risk.

A second, and much less obvious, thought is that we need to re-think our thinking about risk of myocardial infarction with coxibs or NSAIDs and baseline cardiovascular risk in patients. There is less additional risk with coxib or NSAID in the presence of more coronary heart disease risk factors, as we have seen before (Bandolier 137). This may seem counter-intuitive, but it is supported by the finding of no increased heart attacks in meta-analyses of randomised trials in patients with arthritis (generally higher risk), but finding that even low dose aspirin produces higher rates in people with low cardiovascular risk.

There are other comments, of course, notably about accepting the results of any one study with a pinch of salt, however well it seems to be done. The meta-analysis [1] showed quite clearly the spread of results obtained, both with NSAIDs and coxibs. For almost every analysis some studies had significantly lower risk, and others significantly higher. Only for diclofenac and doses of rofecoxib above 25 mg daily were there consistently higher estimates of risk.

Nor should we regard whole populations as being average. Over 2000 years ago the Roman natural philosopher Titus Lucretius was commenting in individual differences, and 100 years ago Archibald Garrold, the British biochemist, was discussing individual differences in drug metabolism. We continue to be sucked into considering average results from trials (the evidence), when few patients are average. The definition of evidence-based medicine is to use the best available evidence to make decisions about individual patients.

Oh, and perhaps as a final comment, we need to consider the matter of making sweeping changes to policy based on inadequate information. Could it be that a lesson is about to be learned? It may well be that decisions that have been taken seemed to be right at the time, but an alternative view might be that they were made on the basis either of too little information, or possible on an inadequate or inappropriate analysis of the information that was available. That is debatable, of course, but it makes for some fascinating thinking about how we assess evidence about adverse events.

References:

1   S Hernández-Díaz et al. Non-steroidal anti-inflammatory drugs and risk of acute myocardial infarction. Basic & Clinical Pharmacology & Toxicology 2006 98: 266-274.
2   F Andersohn et al. Use of first- and second-generation cyclooxygenase-2-selective nonsteroidal anti-inflammatory drugs and risk of acute myocardial infarction. Circulation 2006 113: 1950-1957.
3   LE Lévesque et al. Time variations in the risk of myocardial infarction among elderly users of COX-2 inhibitors, Canadian Medical Association Journal 2006 174: Epub ahead of print. DOI: 10.1503/cmaj.051679

BLINDING REVIEWERS

Just because you are not paranoid doesn't mean that they are not out to get you. People sometimes feel like that if they try to get their papers into certain journals, or abstracts into large and important scientific meetings. At the centre of it all is the peer review process. We accept it is the best we can do, but a study from the US [1] has startling insight into how blinding can affect abstract acceptance.

Study

The study examined submissions for the American Heart Association meetings in 2000 and 2001, where review was open, and 2002-2004, when it was blinded. It was really well done, and the outcome was whether or not a study was recommended for acceptance using standard procedures. Acceptance rates were then judged before and after blining was introduced according to different criteria: US or non-US, English on non-English speaking country, Prestigious or non prestigious institutions, sex of author, US government agency, industry, and by basic or clinical study. Each abstract was evaluated by 8-10 reviewers.

Results

There were over 13,000 abstracts submitted annually, with an average acceptance of 29%. About 40% were from the US, a quarter from highly prestigious institutions. Most (85%) of reviewers were US-based. We might expect higher acceptance from prestigious institutions compared to non-prestigious counterparts, for instance, with open compared with blinded review: if bias were a factor, the gap should narrow with blinding. Table 1 shows that with blinding the gap narrowed by 9%. There were similar changes for abstracts from US government institutions, for US, and for non-industry abstracts. Only sex of author was unaffected.

Comment

However balanced we like to think we are, the simple fact is that we are persuaded that research from government agencies, or prestigious institutions, or not coming from industry, is better. When we are deprived of that information, we make different judgements.

Reference:
1   JS Ross et al. Effect of blinded peer review on abstract acceptance. JAMA 2006 295:1675-1680.

Table 1: The effects of blinding reviewers on abstract acceptance rates - differences in pairs of separate criteria

Criterion	Change (%)
US govt vs non-government	-12.2
Prestigious vs non-prestigious	-8.9
US vs non-US	-8.5
Not industry vs industry	-7.3
English vs non-English	-4.2

ACCEPTING RISK

It is often said that health and safety at work legislation was introduced so that employees were fit to go hang-gliding at the weekend. Bandolier shudders at the thought of leaping off a cliff supported by a thin piece of fabric: it is a risk too far. But what constitutes a risk too far for patients? A study from Boston suggests that many patients are highly risk averse.

Study

Participants were 346 adults presenting at an emergency medicine department in Boston. They were presented with a questionnaire about a hypothetical diagnostic situation as part of a clinical trial, with a series of risk statements. They were asked whether they would agree to have the test or refuse to have the test depending on the statement, or they could indicate that they did not understand the statement.

The test was radioactive Technetium as part of a diagnosis of chest pain to help identify its origin, which could not be determined using standard tests available in the emergency department. The trial involved using the test, already an established and approved procedure, in the emergency department, where its use was considered experimental. Participants were told that the procedure was safe, approved, and used by doctors every day. The six statements said that the risk to them of having the test were:

1   The same as 20 chest x-rays.
2   The same as 10% of the federal limit for occupational radiation workers.
3   The same as five times the natural radiation background received in one year by living in Boston.
4   The same as breathing radon in a house for 2.5 years while living in Boston.
5   The same as the risk of dying from lung cancer by smoking 30 packs of cigarettes.
6   The same as the risk of dying in a car accident from driving 1,500 miles.

Figure 1: Proportion of participants accepting or rejecting participation in a hypothetical trial based on six different statements of equivalent risk

Results

The 346 participants were aged 15 to 82 years, with a median of 34 years, with a mixture of ethnicity and education.

Whatever risk presentation was used, more refused the hypothetical test than accepted it, with differences between presentations (Figure 1). Some (7%) accepted the test with all six presentations, and 16% refused the test with all presentations. Participants with higher educational levels were somewhat more likely to view all the risk presentations as equivalent.

Comment

There are two ways of looking at this. One is as an interesting investigation in different ways of presenting risk. The other is that whatever the presentation, most were put off by any presentation of risk from participating in a sensible study for sensible reasons with probable important implications for their own well being.

To recall, the scenario was that they had come to hospital with chest pain that could not be diagnosed by standard means, and that doctors were asking them to participate in a trial using a safe and approved test involving a small amount of radioactivity that might help make a diagnosis. The only question was where the test might be carried out.

Participants lived in Boston, and several of the risks related to living in Boston, or were related to activities many of them accepted already, like smoking or driving. Yet most of them were averse to accepting even a tiny increase in risk in this situation.

The message appears to be that we don't want any tiny extra risk to interfere with our hang-gliding. The implication just could be that many patients would refuse treatments if told what their risks were. We all need to think about this.

Reference:

1   JA Feldman et al. Evaluating acceptance and understanding risk in the emergency department: are all risk statements created equally? Academic Emergency Medicine 2002 9: 309-316.
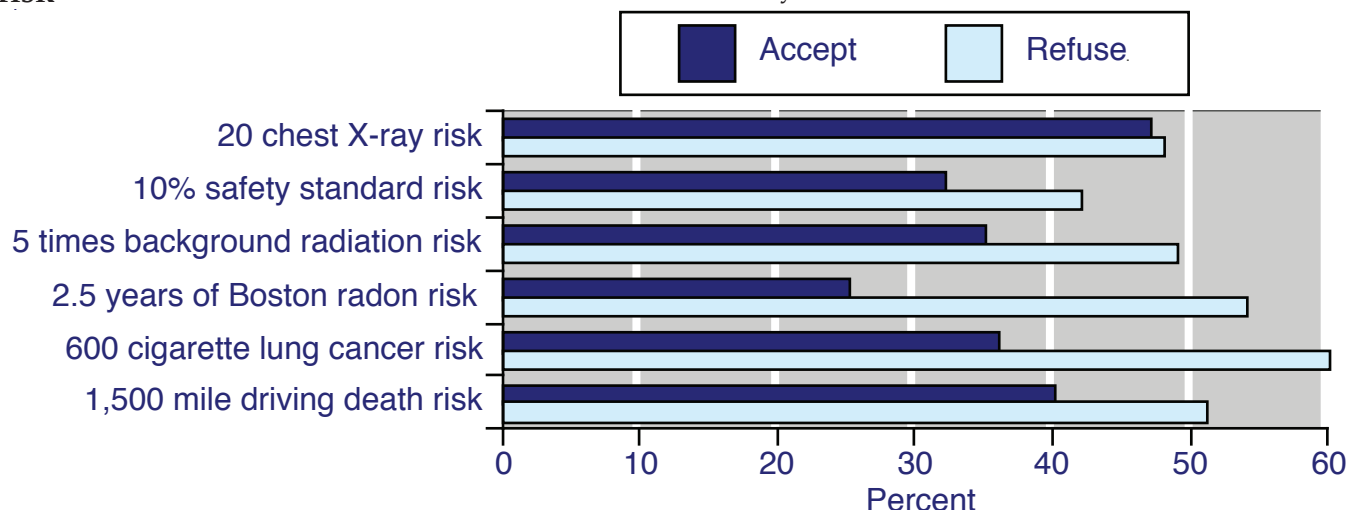
ACTINIC KERATOSIS UPDATE:
IMIQUIMOD AND FLUOROURACIL

Bandolier 143 examined a systematic review of 3% diclofenac gels for treating actinic keratosis. At the time we commented that there are few systematic reviews, but now like buses, several have come along together. Two [1,2] have looked at imiquimod, and two [2,3] fluorouracil, and we can compare these with the evidence available for topical diclofenac.

Imiquimod

One of the reviews [1] has the most detailed descriptions of studies and most trials. It used a thorough literature search using a number of databases and strategies (to August 2005) for randomised trials, and abstracted pre-defined outcomes of efficacy and harm.

It found five randomised placebo (vehicle) comparisons with 1,293 patients, with trial duration of 12-16 weeks. Quality of the trials was high, and they all used one sachet of 5% imiquimod cream applied to lesions on face and balding scalp twice or three times a week.

Complete and partial (>75%) clearance occurred more frequently with imiquimod (Table 1), with numbers needed to treat for complete and partial clearance of 2.2 and 1.8 respectively (Table 1). The three trials that described a formalised lesion count, possibly reflecting higher quality studies, had even lower (better) NNTs of 1.9 and 1.5 for complete and partial clearance.

Local adverse events were more common with imiquimod than vehicle, occurring in 43% of patients. These were mainly erythema (27%), scabbing (21%), flaking (9%), erosion (6%), oedema (4%), and weeping (3%). There were no serious adverse events, and adverse event withdrawals were no more frequent with imiquimod than placebo.

Fluorouracil

The best data comes from a review [2] that was not overtly systematic, but which for fluorouracil contained more trials and patients than a later systematic review [3]. The results in Table 1 relate the efficacy of 0.5% 5-fl;uorouracil in randomised, double blind trials with the outcome of complete clearance after four weeks of therapy. One study found lower rates of clearance with shorter use. This useful review [2] also comments on photodynamic therapy and combination treatments.

Comment

The information we have for all three of the treatments is summarised in Table 1. Clearly, the amount and quality of information available for imiquimod dwarfs that from diclofenac and fluorouracil. For fluorouracil, the worry is that even the little information available comes from studies that would have been excluded from any systematic review using formal quality constraints for included studies.

The imiquimod review also examined adverse events in great detail, and again that gives confidence that information about therapy provided for patients is relevant and useful.

What we have is the usual conundrum of new treatments with good trials well done, and older therapies with little useful information from trials, but backed with experience, and some expectation of some efficacy because of that.

References:
1   G Hadley et al. Imiquimod for actinic keratosis: systematic review and meta-analysis. Journal of Investigative Dermatology 2006. Epub ahead of print. DOI:10.1038/sj.jid.5700264.
2   JL Jorizzor. Current and novel treatment options for actinic keratosis. Journal of Cutaneous Medicine and Surgery 2005 8(Suppl 3):13-21.
2   AK Gupta et al. Evaluation of the effectiveness of imiquimod and 5-fluorouracil for the treatment of actinic keratosis: critical review and meta-analysis of efficacy studies. Journal of Cutaneous Medicine and Surgery 2006. Epub ahead of publication.

Table 1: Summary of efficacy studies of topical imiquimod, 5-fluorouracil, and diclofenac on complete and partial clearance of lesions after end of therapy

Treatment/outcome	Number of		Percent with outcome		NNT (95%CI)
	Trials	Patients	Active	Placebo	
Imiquimod - complete clearance	5	1293	50	5	2.2 (2.0 to 2.5)
Imiquimod - >75% clearance	5	1293	65	11	1.8 (1.7 to 2.0)
Fluorouracil - complete clearance	2	310	51	2	2.0 (1.7 to 2.5)
Diclofenac - complete clearance	2	214	42	16	3.7 (2.6 to 3.6)
Diclofenac - complete clearance including new lesions	3	364	39	12	3.8 (2.8 to 5.5)